NONCLINICAL CONSIDERATIONS: DISPOSITION OF DRUGS

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ABSTRACT

In the design and conduct of pharmacokinetic and toxicokinetic studies, several features should be considered to maximize the utility of the resultant data. Recommendations will be offered regarding the conduct of studies relating the advantages of using the same species, route of administration, and frequency of administration, where possible, as that proposed for pharmacologic and toxicologic testing. The period of dosing should be representative of the proposed clinical duration. Possible “endpoints” to be considered include area under the curve, maximum plasma concentration, volume of distribution, time to maximum plasma concentration, clearance, and half-life of elimination. As suitable, the absolute fraction absorbed should be determined following the administration of the drug at various doses. If a drug will be used under steady state or special physiological conditions, additional pharmacokinetic and toxicokinetic studies if conducted under similar conditions offer useful information. It is also important to evaluate the potential to form metabolites and their contribution to the overall activity profile. Pharmacokinetic and toxicokinetic data has “utility” because it provides a rational and scientific basis crucial to understanding the biological effects of a drug, in identifying and designing appropriate nonclinical studies, and in validating extrapolations between animal studies and humans. Pharmacokinetic and toxicokinetic studies play an integral role in assessing safety and effectiveness.

INTRODUCTION

In the two previous chapters, Drs. Weissinger and Fitzgerald described the value of performing dispositional studies that include pharmacokinetics and toxicokinetics in nonclin-
cal studies. In addition, they have presented examples that illustrate the advantages of collecting these data. Here, I will continue with important considerations regarding the conduct of these studies, useful endpoints, and the application of animal pharmacokinetic and toxicokinetic studies to drug development.

To provide a more rational and scientifically valid approach to the analysis of nonclinical efficacy and safety studies, pharmacokinetic and toxicokinetic studies should be considered based on the intended use of the drug. These kinetic studies make use of concentration and time relationships in determining endpoints useful for understanding the connection between a dose and its biological effects.

**CONDUCT OF STUDIES**

The pharmacokinetics and toxicokinetics of single and repeat dose administrations of a drug are useful tools in the investigation of its biological properties. With the repeated administration of a drug at a given dose, changes may occur in the systemic level of exposure. In some cases, untoward accumulation of a drug may lead to unanticipated toxicities or alterations in various physiological systems. Conversely in some cases, with repeated dosing the systemic levels of a drug may be lowered through increased rates of metabolism or decreased absorption.

Pharmacokinetic and toxicokinetic studies may be conducted either as an integral part of toxicity or efficacy studies or as separate, independent studies. Kinetic studies are often conducted using satellite groups of animals rather than in animals being evaluated for a drug's efficacy or toxicity to avoid confounding variables.

Nonclinical pharmacokinetic and toxicokinetic studies of a new drug are best conducted using the same species, dose range, and route of administration as that used in pharmacological and toxicological studies. A sufficient number of animals should be included at each dose to ensure that inherent variation does not obscure meaningful results in the scientific determination of various kinetic endpoints.

Dosing regimens are important in determining the relationships between a drug, its dose and biological effects. To the greatest extent practical and based on a knowledge of drug disposition, the dosing regimens used in pharmacological and toxicological studies should be representative of those proposed for clinical use.

In larger, non-rodent species, the possibility of once, twice or three times, daily administration may provide sufficient flexibility to mimic levels of drug intended for use in the clinic. Particularly in longer term rodent studies, a practical maximum of twice daily administration of a drug may be the maximum feasible limit on the frequency of dosing. In some cases, an increase in the amount of drug administered per dose may offset the effect of less frequent dosing regimens. Depending upon the absorption and metabolic profile, administration of a drug through the diet may be shown to provide adequate levels of exposure.

The design of kinetic studies should take into account a drug's potential to undergo biotransformation. Where the biological activity of a drug resides in its metabolites, the pharmacokinetics and toxicokinetics of the metabolites may be of more value than that of the